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EXAMINER	
WILLIAMS, LEONARD M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/071,505
Filing Date: February 08, 2002
Appellant(s): HENRIKSEN ET AL.

Craig M. Bohlken
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/25/2007 appealing from the Office action mailed 05/03/2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

The real party in interest in Amersham Health AS (now GE Healthcare AS, a part og General Electric "GE")

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,033,645 UNGER 5-2000

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1,3, 5-7, 11-12, 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger US Patent 6,033,645.

Unger discloses methods of administering a gaseous contrast agent comprising administering the contrast agent and a flushing agent from two different vessels into tubing that enters an upper extremity of a patient. (see figures 1-2; abstract, col 6, line 49-col 7, line 20; col 53, lines 35-67). The rates of infusion of Unger fall within the scope of the instant limitation of claim 1, "controllably," because it falls within the ranges that

are described by Unger (see col 44-47). Unger claims delivery of his contrast agent in a continuous infusion (col 64, lines 20-29). The position of the syringe carrying the contrast agent in Unger is vertical (see figure 1). Unger uses the piston of the syringe as the driver (see element 18 of figure 1).

The flushing agent of Unger is normal saline (col 49, lines 53-55; col 57, line 9).

The flushing step of Unger allows complete transport of the gaseous contrast agent into the bloodstream; thus, at least a portion of the contrast agent of Unger is mixed with the flushing agent of Unger prior to administration into the subject. (col 47, lines 60-col 48, line 10). Unger further explicitly teaches flush rates that fall within the scope of the instant claim 19 (col 48, line 64-col 49, line 25).

Unger claims administration of sulfur hexafluoride and perfluorocarbon filled vesicles such as perflurobutane as his contrast agent (see examples, also col 57, lines 9-21). The vesicles of Unger include albumin-stabilized microbubbles (see col 35, line53-col 36, line 30). Thus, limitations of claims 5-7, 11-12 are also met.

Even though, Unger fails to explicitly recite the instantly claimed infusion period of 5-60 minutes, he explicitly places one of ordinary skill in the art at notice that the rate of administration can be optimized based on the volume of the composition, gaseous vesicles, type of encapsulation and other patient variable such as age, area of interest, etc... Unger makes such statements at numerous places in his patent. For example,

Unger at col 45 states:

> The compositions may be administered over a period of

time which can vary and depends upon a variety of factors including, for example, the volume of the composition being administered, the age and weight of the patient, the particular materials employed in the compositions, including, for example, lipids, polymers, proteins, vesicles, gases and/or gaseous precursors, the purpose for the administration (for is example, diagnostic or therapeutic), the region of interest, the mode of administration, the size of the vesicles (in the case of vesicle compositions), and the like. An exemplary adm/n/strati6n time for the compositions described above is about 5 seconds. Dividing the gas dose by this time period 20 provides a gas administration rate which can be expressed as cc gas/Kg-sec. Thu~ s gas dose of, for example, about $1x10^{-4}$ cc gas/Kg and an administration time of 5 sec provides a gas administration rate of about 2×10^{-5} cc gas/Kg-sec.

It is to be understood that the foregoing specific gas concentrations, composition doses, administration times and administration rates are for purposes of illustration only, and not for purposes of limitation.

Note that Unger states that any exemplified rate is for purposes of illustration not for purposes of limitation. (see col 45, lines 25-28).

At col 47 Unger explicitly states that

> As would be apparent to one skilled in the art, based on the present disclosure, the rate at which the lipid and/or vesicle compositions are preferably administered can vary, depending, for example, on the lipids, polymers, proteins, vesicles, gases and/or gaseous precursors employed, the age and the weight. of the patient, the mode of administration, the size of the vesicles (in the case of vesicle compositions), and the like. Typically, administration may be carried out at lower rates and the rate can be increased until a desired effect is achieved.

Thus, as encouraged by Unger modifying the rate of administration to observe a desired clinical effect is within the scope of the teaching of Unger.

Subsequently, absent a showing of unexpected results, it would have been obvious to one of ordinary skill in the art at the time of invention to optimize the rate of administration of the contrast agent of Unger by routine experimentations and enhance the quality of images, because Unger explicitly recites the rate dependent factors. Thus, one of ordinary skill in the art would have had a reasonable expectation of success in achieving optimal images by determining the optimal rate of infusion.

(10) Response to Argument

Applicant's have further argued the validity of Unger as a 103(a) prior art in reference to the terms "continuous infusion" or "infusion".

The applicant's stated in the remarks of 02/01/2007: "The terms "infusion" or "continuous infusion" is not found in the specification and the claims of WO 97/48337 and also not in the specification of US patent 6,033,645. Hence, the mention of "continuous infusion" was first published on 7th March 2000 which is the publication date of the cited US patent. The instant application claims priority from 27th August 1999, GB 9920392. Applicant therefore holds that US patent 6,033,645 is not valid as 103a prior art with regard to the features related to "infusion" in the instant claims."

The examiner respectfully disagrees. First, in order to accept applicant's assertion the examiner would have to assume the issued patent, its specification and its claims are not valid, and that the examiner of the issued patent issued an invalid patent. The examiner does not see any support for such a position and hence, does not agree with the applicant's assertion. Second, the '645 patent states in col. 51 lines 21-56:

> "In accordance with the embodiment depicted in FIG. 2, the system may be utilized as described hereinafter. The needle (not shown) is inserted into an appropriate blood vessel in the patient (not shown), such as the antecubital fossa vein. The plunger 18' is depressed, causing the contrast agent 20' to be ejected from the syringe 14' into the port 44. The contrast agent 20' will generally pool or collect in the port 44, and may also become distributed throughout the tubing 30'. Since in the present embodiment the contrast agent 20' is not ejected into the patient from the syringe 14', the rate at which the plunger 18' is depressed will

generally not affect the quality of the image obtained during the subsequent diagnostic imaging.

The flush agent 24' is desirably administered after ejection of the contrast agent 20'. This generally involves operation of the control means 42' to drive the mechanical injector 22'. As with the embodiment discussed above, the control means 42' controls the amount of power supplied to the mechanical injector 22' and permits regulation of the rate at which the mechanical injector 22' operates and, thereby, the rate at which the flush agent 24' is ejected from the mechanical injector 22'. The flush agent 24' is ejected from the mechanical injector 22' and into and through the tubing 30' and the port 44. The flush agent 24' serves to push or drive the contrast agent 20 from its location in the port 44 and/or the tubing 30', throughout the length of the tubing 30', and into the patient. Preferably, the mechanical injector 22' is operated, for example, via the control means 42', to provide a flush injection rate of from about 0.05 to about 2 mL/sec. The flush may be stopped after contrast agent 20' has been administered to the patient. Alternatively, the flush may be continued so that the flush agent 24' is also injected into the patient. The rate at which the mechanical injector 22' is operated may be varied at any time during the ejection of the flush agent 24', as desired."

The '645 patent clearly indicates in this section that the flush agent can be administered after the contrast agent and then stopped or the flush may be continued

so that the flush agent is also injected into the patient. This clearly indicates a "continuous infusion". Further evidence that continuous infusion is contemplated is found throughout the specification wherein the administration of the compounds and flush agents are preferably through IV administration either by injection via syringe or by injection via a mechanical injector such as a pneumatic or hydraulic injector.

The examiner wishes to note that the '645 patent and the WO 97/48337 both claim priority to US Application 08/666129 and have identical specifications. As such, the WO document with a publication date of 24 December 1997 supports the use of the terms "continuous infusion" as claimed in the '645 patent.

The applicant's argue that requirement A) or the controllable delivery from an upper extremity of an essentially vertically positioned syringe is not clearly met by the prior art of record (Unger). In response to this the examiner draws attention to Figures 1 and 2 from Unger. The applicant's assert that one can not tell the positioning of the syringe containing contrast agent (20 and 20'; figure 1 and figure 2 respectively) in either of the figures. In Figure 1 the syringe appears to be perpindicular to the patient's lower arm which would mean the syringe containing contrast agent is essentially vertical. Figure 2 appears to show the syringe containing contrast agent (22') essentially vertical to the flush containing syringe and the needle to be placed into the patient's arm.

The applicant's argue that requirement B) or the admixing with a flushing medium prior to administration to the subject is not met by the prior art. The prior art does not teach that at least a portion of contrast agent is mixed with the flushing agent prior to

administration into the subject. The examiner points out the passage quoted below from the '645 patent that clearly shows that the flush agent does indeed mix with contrast agent prior to ejection into the patient. Indeed the flush agent pushes and/or drives the contrast agent forward and into the patient, this entails that the flush agent must interact with the contrast agent prior to ejection into the patient (see Unger col. 51, lines 21-56).

> "The flush agent 24' is desirably administered after ejection of the contrast agent 20'. This generally involves operation of the control means 42' to drive the mechanical injector 22'. As with the embodiment discussed above, the control means 42' controls the amount of power supplied to the mechanical injector 22' and permits regulation of the rate at which the mechanical injector 22' operates and, thereby, the rate at which the flush agent 24' is ejected from the mechanical injector 22'. The flush agent 24' is ejected from the mechanical injector 22' and into and through the tubing 30' and the port 44. The flush agent 24' serves to push or drive the contrast agent 20 from its location in the port 44 and/or the tubing 30', throughout the length of the tubing 30', and into the patient. Preferably, the mechanical injector 22' is operated, for example, via the control means 42', to provide a flush injection rate of from about 0.05 to about 2 mL/sec. The flush may be stopped after contrast agent 20' has been administered to the patient. Alternatively, the flush may be continued so that the flush agent 24' is also injected into the patient. The rate at which the mechanical injector 22' is

operated may be varied at any time during the ejection of the flush agent 24', as desired."

The applicant's argue that requirement C) or delivering the admixed product to the subject over an infusion period of 5-60 minutes is not met by the prior art. The '645 patent clearly indicates in the section described above that the flush agent can be administered after the contrast agent and then stopped or the flush may be continued so that the flush agent is also injected into the patient. This clearly indicates a "continuous infusion". Further evidence that continuous infusion is contemplated is found throughout the specification wherein the administration of the compounds and flush agents are preferably through IV administration either by injection via syringe or by injection via a mechanical injector such as a pneumatic or hydraulic injector. Even though, Unger fails to explicitly recite the instantly claimed infusion period of 5-60 minutes, he explicitly places one of ordinary skill in the art on notice that the rate of administration can be optimized based on the volume of the composition, gaseous vesicles, type of encapsulation and other patient variable such as age, area of interest, etc... Unger makes such statements at numerous places in his patent. For example,

Unger at col 45 states:

"The compositions may be administered over a period of time which can vary and depends upon a variety of factors including, for example, the volume of the composition being administered, the age and weight of the patient, the particular

materials employed in the compositions, including, for example, lipids, polymers, proteins, vesicles, gases and/or gaseous precursors, the purpose for the administration (for is example, diagnostic or therapeutic), the region of interest, the mode of administration, the size of the vesicles (in the case of vesicle compositions), and the like. An exemplary adm/n/strati6n time for the compositions described above is about 5 seconds. Dividing the gas dose by this time period 20 provides a gas administration rate which can be expressed as cc gas/Kg-sec. Thu~ s gas dose of, for example, about $1x10^{-4}$ cc gas/Kg and an administration time of 5 sec provides a gas administration rate of about 2×10^{-5} cc gas/Kg-sec.

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Note that Unger states that any exemplified rate is for purposes of illustration not for purposes of limitation. (see col 45, lines 25-28).

At col 47 Unger explicitly states that

"As would be apparent to one skilled in the art, based on the present disclosure, the rate at which the lipid and/or

vesicle compositions are preferably administered can vary, depending, for example, on the lipids, polymers, proteins, vesicles, gases and/or gaseous precursors employed, the age and the weight. of the patient, the mode of administration, the size of the vesicles (in the case of vesicle compositions), and the like. Typically, administration may be carried out at lower rates and the rate can be increased until a desired effect is achieved."

Thus, as encouraged by Unger modifying the rate of administration to observe a desired clinical effect is within the scope of the teaching of Unger.

Thus all the arguments set forth by the applicant's have been met or are obvious in view of the prior art of record Unger.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Sreenivasan Padmanabhan

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